Treating Posttraumatic Stress Disorder: A Timely Update on Therapeutic Strategies

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Abstract: Posttraumatic stress disorder (PTSD) is a psychological disorder that can develop after an individual experiences or witnesses a traumatic event. PTSD is startlingly common in veterans, victims of assault, those undergoing extreme medical care, and the clinicians that treat them. This growing mental health crisis has been dramatically exacerbated by the stressors and tragic events of the ongoing global COVID-19 pandemic. In this review, we will discuss the different classes of treatment for PTSD and examine current lines of research in each. First, we explore how the field of psychotherapy approaches PTSD, with focus placed on exposure therapy, cognitive behavioral therapy, and more. We then describe current pharmacological strategies for PTSD treatment and several prominent therapeutic strategies currently undergoing clinical and pre-clinical trials. Next, we investigate novel approaches that integrate principles of psychotherapy with seemingly unconventional elements and discuss how these unique components may impact recovery. Finally, we explore how telemedicine has been implemented to expand access to care, which is particularly critical in a time of social distancing and economic disparity. We hope that by summarizing current clinical practice and outlining cutting-edge research, this review can elucidate the field and highlight gaps in knowledge that merit further investigation that may lead to more effective and accessible treatment for PTSD patients.

Keywords: Posttraumatic stress disorder, Contextual memory, Cued memory, Psychotherapy, Pharmacotherapy.

1. INTRODUCTION

Fear is an essential and critical response to stimuli and has been evolutionarily selected to help an animal or individual avoid life-threatening situations. Unfortunately, fear can become maladaptive when it interferes with normal functioning [1]. Fear responses that are either exaggerated or decontextualized from dangerous stimuli can negatively affect an animal by preventing it from acting in its best interest and carrying out the tasks it needs [1]. Many mental disorders revolve around maladaptive memory of fear, and key amongst those is posttraumatic stress disorder, which individuals develop in the wake of experiencing or witnessing a traumatic event [1]. In the weeks and months following trauma, mental symptoms such as intrusive thoughts, nightmares, and flashbacks of the event begin to emerge alongside somatic responses like tachycardia, sweating, insomnia, and stress hormone release [2]. Re-experiencing the event-related cue under this state strengthens the memory's negative valence, making the next reminder potentially worse than the last [3]. Patients experience negative mood, clouded cognition, hypervigilance, sleep disturbance [4], which contributes to the depression and anxiety comorbid with PTSD psychopathology. These symptoms lead to considerable social, occupational, and interpersonal dysfunction.

Although the psychological effects of trauma been noted for ages, trauma-related psychopathology formally drew the attention of the medical community following the epidemics of "shell shock" and "gross stress reaction" following World War I and World War II [5]. Nearly 30% of deployed veterans return home with PTSD, which is elevated dramatically in soldiers spending 12 or more months in a combat zone [6, 7]. PTSD in the military is not only associated with combat. Sexual abuse of women in armed services has drawn increasing attention over recent years, and the effects on survivors are dramatic [8]. In addition, refugees are at particular risk for PTSD that is often the most resistant to treatment [9]. The impact of PTSD extends far beyond active war zones, however. PTSD is startlingly common amongst those facing physical violence, sexual assault, motor vehicle accidents, and those undergoing intensive medical care [8, 10-12]. Women have strikingly higher rates of PTSD symptoms than men, although the underlying mechanisms of this are not fully characterized [13]. Importantly, those witnessing violence and trauma are prone to developing PTSD [14, 15].

With the ongoing COVID-19 pandemic, including patients, healthcare providers, family members, and the public at large are at risk of PTSD due to the

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continuous strain that this has placed on everyone [16-18]. Medical providers and learners also face high burnout rates, making them particularly susceptible to PTSD symptoms and comorbidities [19, 20]. This has resulted in an unsettling prevalence of suicide as a cause of death in the medical field [21]. Amongst men in medical residency, suicide was the leading cause of death. For women residents, suicide was second only to cancer [21].

Because of this grim state of affairs, treatment measures are more critical than ever. In this review, we will explore the different modalities of PTSD treatment currently used in the clinic and those that are the focus of research and clinical trials. Particular emphasis will be taken to elucidate the role of fear-associated memory and fear extinction in PTSD pathology and treatment. Finally, we will examine the impact of the COVID-19 pandemic on PTSD and mental healthcare and explore options that can make healthcare accessible in this time of social distancing and economic distress.

2. FEAR-ASSOCIATED MEMORY AND EXTINCTION

PTSD is fundamentally a state of disordered memory of fear. It is, therefore, essential to discuss how memory of fear works. The three primary components of a fear-associated memory are contextual memory, cued memory, and the physical fight or flight response surrounding the memory [22]. Contextual memory encodes the where and when of a situation, while cued memory refers to the specific stimulus that characterizes the response [22]. For example, suppose an individual is in the grocery store and hears a loud crash from the other aisle. In that case, the grocery store will be encoded as the context, and the crash's sound will be encoded as the cue. A short-term memory trace is generated in the moments following an event [23]. Within the 6 hours, the memory trace is converted into long-term memory in a process called consolidation [23]. This solidifies the memory. Upon memory retrieval, however, the memory trace becomes malleable once again. Remembering an event can elicit feelings, both emotional and physical, and these feelings and thoughts affect the memory trace. Shortly afterward, the memory is once again converted to long-term memory in a process called reconsolidation [23]. This cements the new thoughts associated with the original memory, affecting the valence associated with the experience.

Fear extinction Is the process by which the negative valence of memories regarding the traumatic event is reduced by new memories that are not associated with harm [23-25]**.** If new associative memories regarding a traumatic event are less fearful, this will reinforce that the aversive cue is not dangerous. This approach may be essential to directly target the pathological memory of fear underlying PTSD [25-27]. It is important to note that these processes operate in specific temporal windows. Consolidation takes place in the minutes and first few hours after the experience, as it requires remodeling of the synaptic structure where the memory is encoded. Likewise, reconsolidation takes place in the same timeframe [25]. These time windows are essential for therapeutic targets, as some treatments that target these processes must be delivered in a specific time range to elicit effects, as with the beta-blocker propranolol [25].

In PTSD psychopathology, the balance between cued memory and contextual memory of the traumatic event is disturbed [1, 28]. Cued memory becomes inordinately strengthened in a process called cued hypermnesia [28]. Contextual memory, in contrast, is weakened. This process is called contextual amnesia and is caused by hippocampal hypofunction resulting from extreme stress [28-30]. During trauma-related symptomatic episodes, there is hyperactivation of the amygdala and simultaneous stress hormone release, alongside medial prefrontal cortex disengagement[31]**.** The imbalance of these memories can lead one to feel fear elicited by a trauma-related cue in an environment, or context, that is safe and unrelated from the site of harm [28, 32]. PTSD pathology may be ameliorated by weakening hypermnesia and preserving contextual memory, but more research needs to be done [28, 32, 33]. These different aspects of fear-associated memory are all exploited to treat PTSD and other psychological disorders relating to fear and anxiety [25, 34, 35]. The broadest and most widely used class of treatment for PTSD is psychotherapy [36].

3. PSYCHOTHERAPY

Psychotherapy is the staple form of psychological treatment for PTSD and many other psychological disorders. Defining psychotherapy as a whole, however, is not a simple task. One school of thought states that the many psychotherapy approaches are all unified by the fundamental mechanism of giving patients a context to shape the meaning of their experiences and symptoms to improve the quality of

their lives. However, this is contested by those who believe that each psychotherapy modality has its own distinct, if overlapping, mechanism of action [36]. Despite these disputes, psychotherapy is regarded and implemented as the front-line treatment for trauma-related psychological disorders. The most prevalent form used in the treatment of PTSD patients is exposure therapy.

Exposure therapy is a class of psychotherapy methods that takes advantage of the malleability of fear structure upon re-experiencing to habituate the patient to the anxiety-generating cue to promote the extinction of the fearful reaction [35, 37]. There are many strategies to activate such memories. One such method is prolonged exposure (PE). PE has demonstrated efficacy in treating PTSD and is the leading treatment in the USA [35, 38, 39]. PE is classically performed in multiple sessions over 3 or more months. Sessions entail being exposed to the stimuli in a safe environment with guidance from a trusted therapist who helps the patient discuss and process the emotions and connections between the triggering stimuli and the traumatic event. Exposure is typically limited at first, and increases as time passes and the therapist-client relationship builds [38-40]. Ideally, this results in a less fearful response over time and a resolution of symptoms.

In some cases, the patient can be exposed to the stimuli directly. When this is not feasible or conducive to the patient's wellbeing, there are many other ways by which exposure can be delivered. Imaginal therapy (IE) has the patient imagine and verbalize the memory to trigger re-experiencing. The patient can be encouraged to write out the event's details and their feelings during narrative exposure therapy (NET) [41, 42]. Recent advances in technology have made virtual reality exposure (VRE) feasible, allowing patients to vividly re-experience in 360 degrees and surround sound [43]. VRE was shown to cause reductions in both PTSD and depressive symptoms, but it must be considered that most participants were cisgender men in the military [43]. Another study found that the combination of VRE and D-cycloserine (DCS), a tuberculosis drug, improved the remission rates of PTSD in patients that were traumatized by the 9/11 attacks when compared to VRE+placebo [44].

Another central treatment paradigm for PTSD is cognitive-behavioral therapy (CBT), which explores the relationships between thoughts, feelings, and behaviors to help patients reduce symptoms and develop healthier behaviors. Significant evidence has shown that CBT can improve symptoms and comorbidities of PTSD in many patient cohorts, especially in combination with selective serotonin reuptake inhibitors (SSRIs) [9, 45]. The data surrounding CBT's effects on refugees need further analysis, but results generally suggest positive effects on PTSD symptoms [9]**.** Survivors of severe motor vehicle accidents found that a four week CBT program helped with anxiety and depression, and [12]. Eight weeks of internet-based CBT improved comorbid depression, anxiety, and quality of life in survivors of sexual assault [46]. Interestingly, there was no significant improvement in trauma-related measures in either of these studies. A study that combined 14 sessions of CBT improved PTSD symptoms compared to breathing exercises [47]. This suggests that the source of the trauma, the population involved, and the duration of CBT play a role in its effectiveness.

A more recent development in PTSD treatment is eye movement desensitization and reprocessing (EMDR), which has become hotly sought after for its efficacy and speed of action. EMDR is like exposure therapy in that the patient recounts their traumatic event, but with the addition of structured eye movements, making it a dual attention task. Although there is debate about the underlying mechanisms, this novel therapy practice has demonstrated robust improvement in PTSD symptoms for many patients. Improving the access of EMDR to patients is critical. It involves expanding the reach of training and certification of licensed practitioners. Research investigating Internet-delivered EMDR generated positive yielded, but the sample sizes are too small to draw firm conclusions [48]**.** As well, a greater understanding of its underlying mechanisms may also lead to new avenues of therapy for trauma and fear-related psychological disorders.

4. PHARMACOLOGICAL TREATMENT

The standard approach to pharmacological therapy for PTSD and other psychological disorders, namely major depressive disorder, is the administration of SSRIs, generally in addition to some form of CBT or exposure therapy. Both paroxetine and sertraline are currently indicated for PTSD patients, and several other SSRIs are used off-label [27]. Paroxetine has been found to improve PE's effects on motor vehicle accident victims, and sertraline improved symptoms in

child sexual assault victims when combined with psychotherapy. Unfortunately, even when combined CBT, sertraline did not help refugees, perhaps due to the continuous trauma of displacement and the violence they faced [49]. One limiting factor of SSRIs is the low rate of treatment adherence. Treatment for PTSD takes up to a year, and side effects can include loss of libido, weight gain, and brain fog. This can significantly impair the overall quality of life even while treating PTSD symptoms [27]. Many clinicians believe SSRIs to be semi-interchangeable and often will try multiple SSRIs in succession to figure out the best fit for their patients [27].

As anxiety is a core symptom in PTSD, it is evident that anxiolytic drugs would be studied for therapeutic potential. The benzodiazepine (BZD) family of drugs is a group of classic front-line anxiolytics that work by modulating GABA receptor activity. This increases inhibitory activity, thus decreasing excitatory neurotransmission. Unfortunately, its primary method of action also prevents effective use as a long-term PTSD treatment method. BZD drugs cause a rapid onset of a sedating and sometimes soporific effect, which is not conducive for daily life [50]. As well, BZDs decrease social inhibitions, potentially causing social disruption in one's life. Finally, BZDs are highly habit-forming and must be administered carefully to prevent addiction [50, 51].

BZDs are only one example of an old drug that has been repurposed. The most famous of these for the treatment of PTSD has been propranolol. Propranolol is a beta-adrenergic receptor antagonist that is approved for high heart rate and anxiety. It reduces the peripheral sympathetic nervous system's activity, reducing the somatic sensations of anxiety-like hand tremors and shortness of breath. For this reason, the drug is used off-label by such as surgeons or ballet dancers. Propranolol has differential effects based on when it is applied. When given after an exposure session, propranolol modestly reduced PTSD symptoms [52]. In a breakthrough study from 2018, authors gave patients propranolol 90 minutes before exposure. This led to much larger improvements in PTSD remission. The authors hypothesize that their short session times and treatment timing bypassed extinction and instead targeted reconsolidation [53].

Another repurposed medicine is among the earliest of synthetic drugs, methylene blue (MB). MB is a surgical dye used to identify nerves during surgery and has been used to treat malaria and methemoglobinemia. Patients treated with a combination of MB and DCS, an antibiotic for the treatment of tuberculosis, during prolonged exposure therapy reported a significant improvement in the quality of life compared to placebo [54]. DCS itself is currently in a class 3 clinical trial (NCT02066792). DCS improves the effects of exposure therapy by facilitating fear extinction, effectively speeding up the process in exposure therapy. This improvement, however, diminished over time, so DCS treatment should likely be used during the early stages of treatment for maximum effect [3]. DCS is widely available and may represent an accessible drug that could improve the lives of people with limited medical access.

L-DOPA is the precursor of dopamine and is a mainstay in the treatment of Parkinson's disease. Studies investigating the dopaminergic reward system's role have revealed that boosting dopamine levels may improve fear extinction [55]. L-DOPA administration, which increases central dopamine levels, reduced the time needed for fear extinction and made significant reductions to fear relapse. L-DOPA increased the frequency of spontaneous reactivation of extinction activity in the ventromedial PFC and blunted amygdala activation on a mechanistic level [55-57]. A phase 2 trial is currently being conducted (NCT02560389). If the benefits of treatment outweigh the numerous side-effects of L-DOPA, this widely available drug could be an additional tool in the fight against PTSD. Therefore, it is promising that one study demonstrated that a single administration of L-DOPA restored fear extinction in a mouse model with impaired capacity for fear extinction [55].

Among other drugs currently being assessed in clinical trials for PTSD is the atypical antipsychotic brexiprazole, presently approved for schizophrenia and depression. Its activity on D1 receptors has been demonstrated to help reduce anxiety-like symptoms [58]. Unfortunately, a stage 3 trial for brexiprazole as a monotherapy or adjunct therapy for PTSD was halted due to issues of patient eligibility and safety (NCT01987960). This remains to be confirmed, as there is currently a phase 2 study investigating the drug's safety and efficacy (NCT03033069). Meanwhile, riluzole, an NMDA blocker and anticonvulsant, is presently being studied both as a monotherapy or an adjunct therapy for PTSD [27]. The purported method of action may be through stimulating the release of trophic factors like brain-derived neurotrophic factor

(BDNF) and vascular endothelial growth factor (VEGF) [59].

A variety of novel compounds are being tested in clinical trials as well. Xenon gas inhalation reduces excitability and decreases pro-inflammatory cytokine release, and has been shown to help patients with panic disorders [60, 61]. It is now in a phase 2b/3 trial for PTSD (NCT03635827). In addition, many drugs that target atypical mechanisms are under current investigation. A precursor to the neurosteroid pregnenolone is currently under study in a phase two trial on PTSD symptoms in veterans who fought in Iraq and Afghanistan (NCT03799562). A selective vasopressin receptor antagonist called SRX246 is now in a phase one trial after helping patients with explosive anger deal with aggression and anxiety (NCT02733614) [27, 62]. Finally, endogenous peptide hormones are showing promising results. Oxytocin, oft referred to as "the love hormone," can reduce amygdala activity while increasing activity in the PFC. However, this effect appears to be sex-specific [63]. Neuropeptide Y can mediate anxiety by inhibiting the activity of the amygdala and inhibiting excitatory signaling in the dorsal periaqueductal grey matter [64, 65]. Both of these neuropeptides are currently the subjects of study with promising preliminary data.

Finally, ketamine (NCT02727998), a drug that has been criminalized for recreational use in many locations, is being formally investigated for efficacy and safety in treating PTSD and anxiety-related disorders. Ketamine is an NMDA receptor antagonist that acts as a dissociative anesthetic and hallucinogen and is widely used for animal surgery [27]. In recent years, sub-anesthetic ketamine has been repurposed as an acute treatment for treatment-resistant depression [66, 67]. The underlying mechanism of action is unclear, but through blocking NMDA receptors on GABAergic interneurons, ketamine increases excitatory signaling and stimulates BDNF signaling [68, 69]. A single dose of ketamine significantly abated PTSD symptoms in a double-blinded clinical trial [70]. Currently, several trials are examining multi-dose treatment paradigms. If these are successful, this psychedelic drug may provide quick and powerful relief from PTSD psychopathology.

5. NOVEL APPROACHES AND OTHER METHODS

Pharmacological therapies directly target biochemical neuronal processes to reduce PTSD symptoms. There are other non-pharmacological methods to affect these underlying mechanisms, particularly deep brain stimulation. Deep brain stimulation (DBS) involves the implantation of a device deeply into brain tissue that delivers electric stimulation. This technology is most notably used in the treatment of Parkinson's disorder by stimulating the subthalamic nucleus [71, 72]. There is currently a clinical trial studying the effects of DBS of the basolateral nucleus of the amygdala on PTSD psychopathology (NCT02091843). Preliminary findings have been inconclusive, but one early patient has reported substantial reductions in his severe PTSD symptoms [73]. Unfortunately, there are significant drawbacks to DBS. The process of implanting the electrode entails invasive brain surgery. As well, there are reports that DBS can induce panic attacks in some patients [72, 74]. Regardless, DBS is a promising candidate for the worst of PTSD cases. A non-invasive form of neurostimulation is transcranial magnetic stimulation (TMS), which uses strong magnetic fields to induce a current in a targeted brain region. TMS is currently being used for treatment-resistant depression and is being studied for PTSD [71, 75, 76]. Conclusions are tentative due to inconsistent study design, treatment parameters, and testing criteria. Still, reports generally show beneficial effects on general mental wellbeing and PTSD psychopathology [71, 77]. To truly implement TMS in the clinic, the location of stimulation, treatment schedule, stimulation frequency, and intensity must be defined [75]. One final promising non-invasive technique is transcranial photobiomodulation (PBM), the application of near-infrared light to the head, penetrating through the skull and soft tissue to reach the brain [78, 79]. PBM works by stimulating mitochondrial cytochrome c oxidase, increasing cellular energy stores, and promoting trophic factor release while reducing inflammatory factors and cell death [78, 79]. In a study focusing on TBI, PTSD symptoms related to the cause of injury were reduced after 18 outpatient treatments spread out over 8 weeks [80]. Based on these preliminary findings, a pilot study is underway to investigate PBM's potential for PTSD treatment [80, 81]. Perhaps these treatment methods may one day be used in the clinic as monotherapies or, more likely, adjuncts to psychotherapy.

One novel form of psychotherapy is equine psychodynamic psychotherapy, which uses horses as an emotional transference object. The mutual trust between the therapist and the horse is used to create a network of mutual obligation. This approach seems to

have merits and is novel in a way that may attract people who may be unmotivated to pursue other forms of psychotherapy; however, there is not yet enough evidence to unequivocally support its efficacy in treating PTSD [5, 82]. Regardless, the strong bond between humans and horses has repeated itself across human history, so there is good reason to believe it be beneficial to mental wellbeing.

The therapeutic properties of music have also been noted for millennia. Still, the practice of music therapy has only been codified since the formation of the National Association for Musical Therapy in 1950. This came after music was used with positive effects in the treatment of PTSD, then called "shell shock" in soldiers returning from WWI and WWII. Modern musical therapy is defined as "clinical, evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program" [5, 82]. Military providers most often perform musical therapy as both a monotherapy and adjunct treatment for PTSD, TBI, and MST patients and some with physical injuries.

Music therapy can occur in group settings for social symptoms and loneliness, and in single-person sessions for speech issues and mood disorders. The most common form of musical therapy is music-making through drumming. Music therapy has been widely deemed effective in improving mood and addressing symptoms, but more evidence is needed to establish its efficacy [5, 82]. First, higher power evidence from studies with standardized protocols is required. Additionally, there is a gender bias towards male patients, especially in military settings. This does a disservice, especially towards women, who often suffer the brunt of military sexual abuse. Finally, there needs to be research to identify specific interventions for specific disorders and symptoms [5, 82].

There are many approaches that explore novel techniques. CBT has been combined successfully with breathing biofeedback training [83]. Mindfulness training and yoga helped women with interpersonal violence trauma [84, 85]. Somatic experience, a bodily engagement technique, reduced PTSD severity and depression. Somatic awareness can also be improved with neurofeedback and aerobic exercise, the latter of which has marked effects on depression and anxiety disorders [86, 87]. These techniques only scratch the surface of innovative approaches to PTSD management, and further study will only broaden the toolset to treat trauma victims.

6. COVID-19, TELEMEDICINE, AND ACCESSIBILITY

In general, it is both expensive and inconvenient to gain access to effective psychotherapy, especially in the time of COVID-19. The shift towards telemedicine has decreased the inconvenience and barrier of access to transportation, but rising unemployment has left many with health insurance. Therefore, many people are turning to free alternatives. One set of such alternatives are psychotherapy apps for smartphone devices [88]. While this option does sound promising, there are several limitations to this approach. First, there is an oversaturation in the marketplace. As of 2020, 555 apps are categorized by their creators as therapy tools, according to Sander *et al*. 69 apps fulfilled their inclusion criteria, and only 1 was actually evaluated in a random trial. Most were based on CBT [88]. Additionally, there are privacy concerns for many of these apps. Considering that many people eschew therapy due to a lack of trust in the patient-clinician relationship, this poses another significant drawback to this option [89]. It is possible that if mental health crisis centers are given information regarding effective and safe therapy apps; however, this may yet be a viable option to expand access to care. Still, more evidence-based options are needed, and there should be clear indications on the app store to help consumers and potential patients make safe and effective decisions.

There have been other attempts to deliver therapy to patients digitally. Trauma-focused CBT has been shown to reduce PTSD symptoms in digital settings [90]. In addition, there has limited but encouraging work detailing the effective application of online EMDR therapy [91]. In most studies, online versions of different treatments tend to be more effective than either waitlist and self-help, but whether they match the quality of their offline versions remains to be seen [35]. Regardless, the work done included patients of many different backgrounds and sources of trauma, a feature that is lacking in many other studies. Finally, there is an untapped market of using online VR spaces for traditional therapy options, although this does limit treatment to those with expensive at-home VR units. More research may identify the most effective forms of telemedicine, which will undoubtedly expand the range of patients receiving life-saving therapy for their PTSD symptoms in the current prolonged COVID-19 pandemic or others we will face in the future.

7. CONCLUSION

PTSD pathology is complex and multifactorial and requires an expansive toolset of therapeutic options to manage the diverse population of PTSD patients. In general, it appears that various forms of exposure therapy are by and large the standard treatment. However, CBT and EMDR are often used with great effect. Pharmaceuticals are also in use, but they are nearly exclusively prescribed as an adjunct treatment alongside some form of psychotherapy. Many new and old drugs are being investigated in clinical and pre-clinical trials, ranging from classic SSRIs to Xenon gas. Finally, the pressures of the COVID-19 epidemic have hastened the adaptation of telemedicine applications of psychotherapy and will most likely play outsized importance in the coming future.

Adapting these therapies to encompass more patients and maintain the recovery of current patients is of the upmost importance. In drug discovery, great importance must be paid to the side effects of any drug given, as adverse effects are often the cause of drug adherence. Additionally, clinical psychotherapy will have to adapt to the digital ecosystem, especially as patients emerge from generations who were online from their early childhood. While social media and the internet have caused problems, both personal and societal, they provide an opportunity to understand and adapt to this generation. Perhaps the openness of Millennials and Gen Z to mental health topics will spur this advance as they become clinical practitioners on their own and adapt their experiences into the future of psychotherapy. If these insights, combined with the latest research advances, prove fruitful, the future of PTSD treatment could be characterized by accessibility and efficacy for all.

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